Chemistry of Heterocyclic Compounds, Vol. 41, No. 4, 2005

SYMMETRICAL AND UNSYMMETRICAL BIS-1,1'-(3,4-DIHYDROISOQUINOLINES)

V. A. Glushkov, V. I. Karmanov, and Yu. V. Shklyaev

3,3,-Dialkyl-1-cyano-3,4-dihydroisoquinolines were prepared by Beckmann defragmentation of ethyl α-(3,3-dialkyl-3,4-dihydroisoquinol-1-yl)-α-hydroximinoacetates and they take part in a Ritter reaction to form substituted bis-1,1'-(3,4-dihydroisoquinolines).

Keywords: bis-1,1'-isoquinolines, isoquinoline, nitriles, oximes, Beckmann rearrangement, Ritter reaction.

As heterocyclic analogs of 1,1'-binaphthyl systems, bis-1,1'-isoquinolines are promising ligands for the preparation of metallocomplex catalysts since coordination with a metal is possible at the nitrogen atoms [1]. A method is known for the Ullman preparation [2] of bis-1,1'-isoquinolines while 3,4-dihydro derivatives are not formed under these conditions and they are rather inaccessible compounds. Bis-1,1'-(3,4-dihydroisoquinolines) unsubstituted in position 3 have been previously obtained using a Bischler–Napieralski reaction by the action of $POCl_3$ in acetonitrile [3] or Tf_2O in the presence of 4-N,N-dimethylaminopyridine [4] on the corresponding oxamide. In the current work we propose a route to bis-1,1'-(3,4-dihydroisoquinolines) which is based on the Ritter reaction [5, 6].

A second order Beckmann rearrangement [7, 8] of ethyl α-(3,3-dialkyl-3,4-dihydroisoquinol-1-yl)-α-hydroximinoacetates **1a-c** using the method [9, 10] gave the nitriles **2a-c**. Despite the simplicity it should be noted that the indicated method is poorly reproducible in our hands, the yields of the products **2** differing markedly from one experiment to another.

The nitrile **2a** was also prepared by the dehydration of 3,3-dimethyl-3,4-dihydroisoquinolylaldoxime **3** [11] in refluxing xylene using a known method [12] (see Experimental section. The hydrochloride **3**.HCl has been reported before [13]).

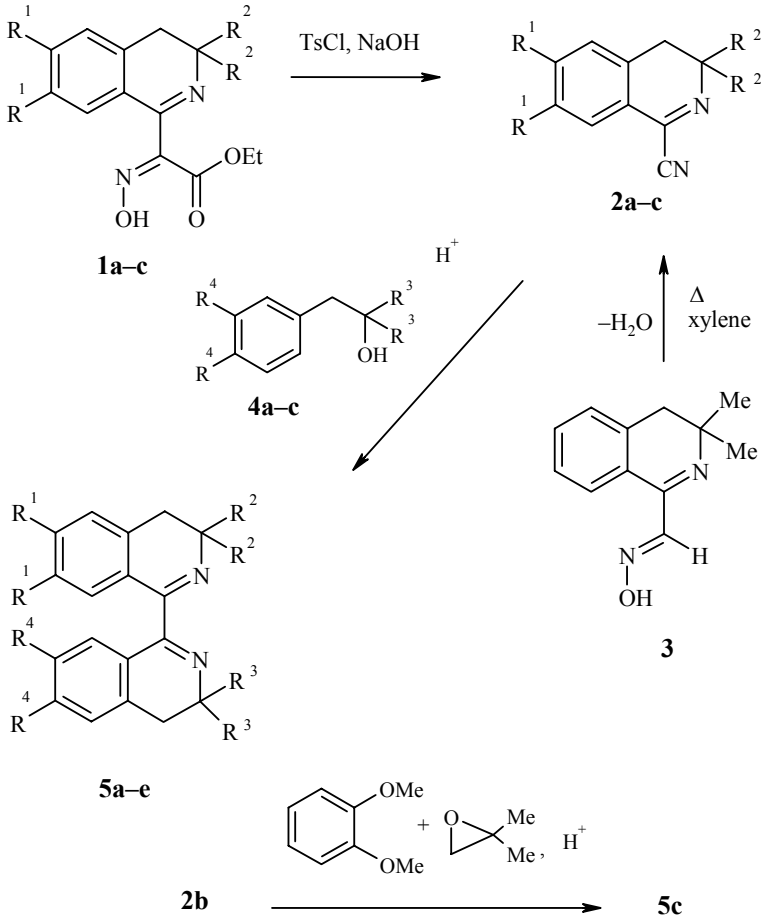
The Ritter reaction of nitriles **2a-c** and carbinols **4a-c** (stirring the reagents in a mixture of toluene and conc. H_2SO_4 at 20°C) gave 42-71% yields of compounds **5a-e** (Tables 1 and 2). According to this scheme another combination of nitrile and carbinol is possible which leads to both symmetrical and unsymmetrical bis-1,1'-(3,4-dihydroisoquinolines) **5**. Compound **5c** was also prepared in somewhat lower yield (37%) by the condensation of nitrile **2b** with veratrole and isobutylene oxide using method [14] (Scheme 1).

A feature of the ^1H NMR spectrum of compound **5b** is the small shift of the H-8 signal of the 6,7-dimethoxy-substituted ring to high field by about 0.2 ppm when compared with the H-8 signal of 6,7-dimethoxy-1,3,3-trimethyl-3,4-dihydroisoquinoline [14] and this is due to the anistropic effect of the neighboring 3,4-dihydroisoquinoline fragment. A similar high field shift caused by a benzene ring has previously been observed by us in the case of 6,7-dimethoxy-3,3-dimethyl-1-phenyl-3,4-dihydroisoquinoline [14].

Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, Perm 614990; e-mail: cheminst@mpm.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 558-563, April, 2005. Original article submitted March 12, 2002; revision submitted July 23, 2003.

0009-3122/05/4104-0475

Scheme 1



1, 2 a R^1 = H, R^2 = Me; **b** R^1 = OMe, R^2 = Me; **c** R^1 = H, $R^2 + R^2 = (CH_2)_5$;
4 a R^3 = Me, R^4 = H; **b** R^3 = Me, R^4 = OMe, **c** $R^3 + R^3 = (CH_2)_5$, R^4 = H;
5 a $R^1 = R^4$ = H, $R^2 = R^3$ = Me; **b** R^1 = H, $R^2 = R^3$ = Me, R^4 = OMe;
c $R^1 = R^4$ = OMe, $R^2 = R^3$ = Me; **d** $R^1 = R^4$ = H, R^2 = Me, $R^3 + R^3 = (CH_2)_5$;
e R^1 = OMe, R^2 = Me, $R^3 + R^3 = (CH_2)_5$, R^4 = H

As a result of the transannular interaction between the H-8 and H-8' protons, the bis-1,1'-isoquinoline molecule is not overall planar but the rotation barrier for its bicyclic fragments is not high enough to form separate atropoisomers [15]. Fixing of the latter permits complex formation with Ru(II) or Os(II) [16, 17]. Introduction of a substituent into position 8 increases the energetic barrier to rotation and hence for 8,8'-dialkyl-1,1'-bisisoquinolines also makes possible the formation of atropoisomers [18-20].

In order to resolve the question of the steric structure of the substituted bisisoquinolines **5a-e** we carried out quantum-chemical calculations and X-ray analysis of compound **5a**. Optimization of the geometry using the MM2 molecular mechanics method and subsequent minimization of the energy using the semiempirical AM1 method (Hyperchem 5.01 trial version package [21]) led to a structure in which both isoquinoline fragments are almost perpendicular, the angle between the planes being 84.3° in the case of compound **5a** and 81.4° for **5c** which is close to the calculated angle for 8,8'-diethyl-1,1'-bisisoquinoline (93.8°) [19]. Crystals of compound **5a** have space group 2*C*/*c* with *Z* = 8. According to X-ray data the length of the bond between the two isoquinoline fragments in compound **5a** is 1.513 Å and the angle between them 90.0°. Detailed X-ray results for compound **5a** will be published in a specialist article.

TABLE 1. Characteristics of Compounds **2a-c, 5a-e**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (recrystallization solvent)	Yield, % (method)
		C	H	N		
2a	$C_{12}H_{12}N_2$	78.37 / 78.23	6.64 / 6.56	15.03 / 15.20	56-58 (DMF–water)	76 (A) 36 (B)
2b	$C_{14}H_{16}N_2O_2$	68.91 / 68.83	6.56 / 6.60	11.30 / 11.47	85-86 (hexane)	96
2c	$C_{15}H_{16}N_2$	80.70 / 80.32	7.22 / 7.19	12.65 / 12.49	53-55 (petroleum ether)	88
5a	$C_{22}H_{24}N_2$	83.79 / 83.50	7.82 / 7.64	9.07 / 8.85	119-121 (MeOH–water)	49
5b	$C_{24}H_{28}N_2O_2$	75.52 / 75.56	7.55 / 7.50	7.47 / 7.44	157-158 (MeOH–water)	59
5c	$C_{26}H_{32}N_2O_4$	72.03 / 71.53	6.55 / 6.47	6.70 / 6.41	189-190 (EtOH–water)	60 (A) 37 (B)
5d	$C_{25}H_{28}N_2$	84.04 / 84.22	7.88 / 7.92	7.91 / 7.86	131-132 (MeOH–water)	71
5e	$C_{27}H_{32}N_2O_2$	77.91 / 77.85	7.60 / 7.74	6.83 / 6.72	125-127 (hexane)	32

TABLE 2. Spectroscopic Characteristics of Compounds **2a-c, 5a-e**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm				Mass spectrum, $[M]^+$ (I_{rel}, %)
		R^1, R^4 (OCH_3)*	R^2, R^3	2H-4 and 2H-4'	H_{arom}	
1	2	3	4	5	6	7
2a	2235 (w, C≡N), 1680, 1600, 1565, 1275, 1255, 1205, 1175, 1120, 1040, 1030, 1020, 970, 950, 925	—	1.25 (6H, s, $2CH_3$)	2.83	7.28-7.68 (4H, m)	184 (70)
2b	2340 (w, C≡N), 1600, 1565, 1520, 1285, 1275, 1250, 1230, 1205, 1145, 1040, 980	3.83 (3H, s), 3.87 (3H, s)	1.21 (6H, s, $2CH_3$)	2.74	6.90 (1H, s, H-5), 7.05 (1H, s, H-8)	244 (78)
2c	2340 (w, C≡N), 1685, 1600, 1565, 1340,1290, 1270, 1185, 1135, 1045, 1025, 980, 965	—	1.40-1.75 (10H, m, $5CH_2$)	2.82	7.30-7.62 (4H, m)	224 (100)
5a	1625, 1570 (w), 1245, 1175, 1040 (w), 940	—	1.26 (12H, s, $4CH_3$)	2.84	7.14-7.30 (6H, m, H-5,5',6,6',7,7'), 7.39 (2H, m, H-8,8')	316 (47)
5b	1605, 1565, 1515, 1275, 1250, 1230, 1200, 1175, 1155, 1130, 1110, 1060, 935, 845	3.60 (3H, s), 3.85 (3H, s)	1.23 (6H, s, $2CH_3$), 1.28 (6H, s, $2CH_3$)	2.75 2.83	6.82 (1H, s, H-5), 6.87 (1H, s, H-8), 7.18-7.23 (3H, m, H-5',6',7'), 7.37 (1H, m, H-8')	376 (58)
5c	1600, 1565, 1620, 1340, 1275 (s), 1235, 1200, 1125, 1035, 1005, 930, 910, 845	3.61 (6H, s), 3.83 (6H, s)	1.25 (12H, s, $4CH_3$)	2.72	6.83 (2H, s, H-5,5'), 6.87 (2H, s, H-8,8')	436 (34)

TABLE 2 (continued)

1	2	3	4	5	6	7
5d	1620, 1565, 1345, 1290, 1240, 1225, 1175, 980, 940	—	1.27 (6H, s, $2CH_3$), 1.50 (6H, m, $3CH_2$) 1.69 (4H, m, $2CH_2$)	2.84	7.13-7.30 (6H, m, H-5,5',6,6',7,7'), 7.39 (2H, m, H-8,8')	356 (100)
5e	1605, 1570, 1515, 1340, 1275, 1235, 1200, 1160, 1230, 1155, 1125, 1060, 1040 (w), 1000 (w), 930, 865	3.60 (3H, s), 3.84 (3H, s)	1.22 (6H, s, $2CH_3$), 1.50 (6H, m, $3CH_2$), 1.70 (4H, m, $2CH_2$)	2.74 (2H) 2.82 (2H)	6.82 (1H, s, H-5), 6.86 (1H, s, H-8), 7.15-7.28 (3H, m,H-5',6',7'), 7.35 (1H, m, H-8')	416 (100)

* Signals for R^1 = H and R^4 = H are given in the H_{arom} column.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument for suspensions in vaseline oil and ^{1}H NMR spectra at 25°C on a Bruker WM-250 spectrometer (250 MHz) using DMSO-d_6 solvent and HMDS internal standard with δ = 0.05 ppm. Mass spectra were taken on a Finnigan MAT instrument under standard conditions (EI, 70 eV). Monitoring of the reaction course and the purity of the products obtained were performed using TLC on Silufol plates using chloroform–acetone (9:1) and revealed using 3% chloranil in toluene.

Oximes **1a,b** and **3** were synthesized as described before ([22], [23], and [11] respectively). The carbinol **4a** was an Aldrich product. Carbinols **4b** and **4c** were synthesized using a Grignard reaction as described before ([25] and [26] respectively). The parameters agreed with those reported in the literature for samples **4b** [27] and **4c**[26].

Ethyl α-Hydroximino(3,3-pentamethylene-3,4-dihydroisoquinol-1-yl)acetate (1c) was prepared by the nitrosation of ethyl (3,3-pentamethylene-1,2,3,4-tetrahydroisoquinolyliden-1)acetate [6] using sodium nitrite in AcOH using a known method [24]. Yield 65%; mp 138-139°C (toluene–hexane). According to the ^{1}H NMR data the oxime **1c** is formed as a mixture of the *Z*- and *E*-isomers (ratio 4:3 or 3:4, the predominant isomer not being established). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 and 1.24 (3H, two t, *J* = 7.2, CH_3); 1.30-1.72 (10H, m, 5 CH_2); 2.67 and 2.73 (2H, two s , CH_2-4); 4.21 and 4.25 (2H, two q, *J* = 7.2, OCH_2); 7.00 and 7.95 (1H, two d, *J* = 9.0, H-8); 7.22-7.45 (3H, m, H-5,6,7); 12.15 and 12.31 (1H, two s, OH). Found, %: C 68.54; H 5.69; N 13.57. $C_{18}H_{22}N_2O_3$. Calculated, %: C 68.77; H 5.77; N 13.36.

3,3-(R^2)$_2$-1-Cyano-6,7-(R^1)$_2$-3,4-dihydroisoquinolines 2a-c. A. Oxime **1a** (2.74 g, 10 mmol) and *p*-toluenesulfonyl chloride (1.90 g, 10 mmol) were added successively to acetone (100 ml) at 50°C. NaOH (10%, 16 ml) was added to the solution in a single aliquot and the mixture was refluxed for 1 h. About 60 ml of acetone was removed from the reaction mixture, the residue was poured into water, and the mixture obtained was extracted with chloroform. The extract was washed with water and dried over $MgSO_4$ and the residue after distillation of chloroform was recrystallized from methanol (-20°C) and then from aqueous DMF (60% by volume). Evaporation gave the nitrile **2a** (1.39 g).

Nitriles **2b,c** were prepared similarly from the oximes **1b,c** and purified by recrystallization (Table 1).

B. Oxime **3** (1.01 g, 5 mmol) was refluxed in *p*-xylene (30 ml) for 3 h, the xylene was evaporated in vacuo, the residue was dissolved in hexane, and the crystals were filtered off and recrystallized similarly to method A to give the nitrile **2a** (0.33 g) which was identical to that prepared by method A (IR spectrum, ^{1}H NMR data, R_f, mp).

3,3-(R^2)$_2$-6,7-(R^1)$_2$-3',3'-(R^3)$_2$-6',7'-(R^4)$_2$-Bis-1,1'-(3,4-dihydroisoquinolines) 5a-e. A. A solution of nitrile **2b** (0.3 g, 1.23 mmol) and carbinol **4a** (0.2 ml, 1.25 mmol) in toluene (20 ml) was added to conc. H_2SO_4 (10 ml) and the mixture obtained was stirred for 2 h at 20°C and poured into water (100 ml).The aqueous layer was separated, washed with toluene (15 ml) and NH_4OH (25%) was then added to pH ~ 8. The product was extracted with CH_2Cl_2 and the extract was washed with water, dried over $MgSO_4$, the solvent was distilled off, and the residue was recrystallized to give compound **5b** (0.27 g). Similarly, combination of nitriles **2a-c** and carbinols **4a-c** gave compound **5a** (**2a**+**4a**), **5c** (**2b**+**4b**), **5d** (**2c**+**4a**), and **5e** (**2b**+**4c**).

Crystals of the product **5a** were formed after basification of the aqueous solution and holding the mixture obtained for 3 h and they were filtered off, washed with water, and recrystallized. In the synthesis of product **5c** the oily residue after distillation of CH_2Cl_2 was triturated with ether to give a solid which was crystallized from aqueous methanol. Compound **5e** was separated similarly to **5b**, the residue after distillation of solvent being extracted with hot hexane and the extract filtered to give pure (by TLC) crystals of compound **5e** precipitating from the filtrate in the cold.

Synthesis of Compound 5c. B. A solution of the nitrile **2b** (0.5 g, 2 mmol), veratrole (0.26 ml, 2 mmol), and isobutylene oxide (0.2 ml, 2.2 mmol) in toluene (10 ml) was added dropwise to H_2SO_4 (98%, 10 ml), stirred for 1 h, poured into water (100 ml), and treated further as described in method A. Yield of the product **5c** 0.32 g.

The work was carried out with the financial support of the Russian fund for basic research (project No. 01-03-96479).

REFERENCES

1. N. W. Alcock, D. I. Hulmes, and J. M. Brown, *J. Chem. Soc. Chem. Commun.*, 395 (1995).
2. K. Yamamoto, H. Tateishi, K. Watanabe, T. Adachi, H. Matsubara, T. Ueda, and T. Yoshida. *J. Chem. Soc. Chem. Commun,* 1637 (1995).
3. G. K. Cheung, I. M. Downie, M. J. Earle, H. Heaney, M. F. S. Matough, K. F. Shuhaibar, and D. Thomas, *Synlett.*, 77 (1992).
4. M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, D. C. R. Hockless, J. W. Holman, R. W. Read, and A. W. Wu, *J. Chem. Soc. Chem. Commun.*, 2551 (1995).
5. H. Wollweber and R. Hiltman, *Angew. Chem.*, **72**, 1001 (1960).
6. V. C. Skhlyaev, B. B. Aleksandrov, G. I. Legotkina, M. I. Vakhrin, M. S. Gavrilov, and A. G. Mikhailovskii, *Khim. Geterotsikl. Soedin.*, 1560 (1983).
7. Houben-Weil, *Methoden der Organischen Chemie*, Vol. 10, Georg Thieme Verlag, Stuttgart, New York (1968), Part 4, p. 228
8. L. G. Donaruma and W. Z. Heldt, in *Organic Reactions* [Russian translation], Vol. 11, Inostr. Lit., Moscow (1965), p. 7.
9. A. P. Stankyavichus, P. B. Terent'ev, and O. A. Solov'ev, *Khim. Geterotsikl. Soedin.*, 509 (1971).
10. A. P. Stankyavichus, L. M. M. Stankyavichene, and P. B. Terent'ev, *Khim. Geterotsikl. Soedin.*, 1462 (1999).
11. B. B. Aleksandrov, M. S. Gavrilov, V. D. Sviridov, N. D. Chkanikov, V. S. Shklyaev, and Yu. V. Shklyaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2136 (1990).
12. Yu. V. Shklyaev, B. Ya. Syropyatov, and V. S. Shklyaev, *Bashk, Khim. Zh.*, **4**, No. 4, 21 (1997).
13. E. A. Mistrukov, Y. Rozpravra, and O. N. Sorokina, *Mendeleev Commun,*, 205 (1993).
14. V. A. Glushkov and Yu. V. Shklyaev, *Mendeleev Commun.*, 17 (1998).
15. M. T. Ashby, G. N. Govindan, and A. K. Grafton, *J. Am. Chem. Soc.*, **116**, 4801 (1994).
16. M. T. Ashby, *J. Am. Chem. Soc.*, **117**, 2000 (1995).

17. G. Chelucci, A. Bacchi, D. Fabbri, A. Saba, and F. Ulgheri, *Tetrahedron Let.*, **40**, 553 (1999).
18. G. Chelucci, M. A. Cabras, A. Saba, and A. Sechi, *Tetrahedron: Asymmetry*, 1027 (1996).
19. H. Tsue, H. Fujinami, T. Itakura, R. Tsuchiya, K. Kobayashi, H. Takhashi, and K. Hirao, *Chem. Lett.*, 17 (1999).
20. H. Tsue, H. Fujinami, T. Itakura, and K. Hirao, *Tetrahedron: Asymmetry*, **10**, 2975 (1999).
21. L. J. Chiang, J. W. Swirczewsc, K. Liang, and J. Millar, *Chem. Lett.*, 981 (1994).
22. V. S. Shklyaev, B. B. Aleksandrov, and M. S. Gavrilov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 959 (1986).
23. Yu. V. Shklyaev, V. A. Glushkov, V. V. Davidov, V. I. Sokol, and V. S. Sergienko, *Mendeleev Commun.*, 36 (2000).
24. Yu. V. Shklyaev, B. Ya. Syropyatov, V. S. Shklyaev, M. S. Gavrilov, E. S. Boronenkova, R. Z. Dautova, B. B. Aleksandrov, and A. A. Gorbunov, *Khim.-Farm. Zh.*, **33**, No. 9, 8 (1999).
25. J. M. Bruce and A. Chaudhry, *J. Chem. Soc. Perkin Trans. 1*, 372 (1972).
26. P. Sabatier and A. Mailhe, *C. R. Acad. Sci.*, **138**, 1321 (1904).
27. A. Arcoleo, M. C. Natoli, and M.-L. Marino, *Ann. Chim. (Ital).*, **60**, 323 (1970); *Ref. Zh. Khim.*, 24Zh334 (1970).